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ERRATA

SPECIFICATION No. 860,303

Page 2, lines 54 and 55, *for* "otherosclerosis"
read "atherosclerosis"

Page 8, line 56, *for* "temperature" *read* "tem-
peratures"

THE PATENT OFFICE
9th December 1968

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

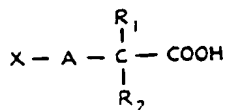
Pharmaceutical Compositions comprising α -Aryloxy-Aliphatic Carboxylic Acids and/or α -Arylimino-Aliphatic Carboxylic Acids, their Esters and Salts

5 We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to new pharmaceutical compositions and more particularly it relates to pharmaceutical compositions which possess valuable therapeutic properties.

15 It is believed that certain diseases such as coronary artery disease and atherosclerosis in man are associated with an abnormally high concentration of cholesterol in the blood serum. We have now found that certain aryl derivatives of aliphatic acids reduce the concentration of cholesterol in the blood serum, and they may therefore be useful in the treatment of such diseases as coronary artery disease and atherosclerosis.

20 According to the invention we provide pharmaceutical compositions containing as active ingredient at least one compound of the formula:—



30 wherein A stands for oxygen or for the amino radical, R₁ and R₂, which may be the same or different, stand for hydrogen or for alkyl radicals or they may be joined to form, together with the adjacent carbon atom, a cycloalkyl ring, and X stands for a phenyl or naph-

[Price 3s. 6d.]

thyl radical which may optionally be substituted by one, two or three substituents which may be the same or different and which are selected from halogen atoms and alkyl, alkenyl, alkoxy, aryl, aralkyl, aralkoxy and arylamino radicals, or the esters or salts thereof, together with a pharmaceutically-acceptable inert diluent or carrier, provided that the inert diluent or carrier is not water or an organic solvent.

As particularly suitable alkyl radicals (R₁ and R₂) there may be mentioned for example methyl and ethyl radicals, and a suitable cycloalkyl ring may be the cyclohexane ring. Preferred esters of the above described acids are the methyl, ethyl and *n*-propyl esters and suitable salts of the said acids may be the alkali metal or alkaline earth metal salts such as the sodium, potassium or calcium salts or, when the acids possess a strongly basic substituent, the acid-addition salts thereof such as the hydrochlorides.

Preferred compounds to be used as the active ingredient in the compositions of the invention are *p*-chlorophenoxyisobutyric acid and the esters and salts thereof such as the methyl, ethyl and *n*-propyl esters, and the alkali metal and alkaline earth metal salts such as potassium salt, which is soluble in water, and the calcium salt, which is sparingly soluble in water. As examples of other active ingredients within the scope of this invention there may be mentioned the following acids and/or their esters or salts:—

phenoxyisobutyric acid; 2-methylphenoxyisobutyric acid; 3-methylphenoxyisobutyric acid; 4-methylphenoxyisobutyric acid; 2-chlorophenoxyisobutyric acid; 3-chlorophenoxyisobutyric acid; 4-bromophenoxyisobutyric

- acid; 2:4-dichlorophenoxyisobutyric acid; 2:4:5-trichlorophenoxyisobutyric acid; 3:4-dimethylphenoxyisobutyric acid; 4-methoxyphenoxyisobutyric acid; α -naphthoxyisobutyric acid; β -naphthoxyisobutyric acid; α -(p-chlorophenoxy) α -methyl-n-butyric acid; α -(p-chlorophenoxy)propionic acid; α -(p-chloroanilino)isobutyric acid; 1-anilinocyclohexane carboxylic acid; 4-ethylphenoxyisobutyric acid, m.p. 77—78° C.; 4-tertiary butylphenoxyisobutyric acid, m.p. 93—94° C.; 4-phenylphenoxyisobutyric acid, m.p. 167—168° C.; 4-tertiary octylphenoxyisobutyric acid, m.p. 89—90° C.; 2-methoxyphenoxyisobutyric acid, m.p. 45—47° C.; 3-methyl-4-chlorophenoxyisobutyric acid, m.p. 85—86° C.; ethyl 2-methoxy-4-allylphenoxyisobutyrate, b.p. 118—120° C./0.2 mm.; ethyl 2-benzyl-phenoxyisobutyrate, b.p. 152—156° C./0.4 mm.; ethyl 3:4-dichlorophenoxyisobutyrate, b.p. 104° C./0.2 mm.; ethyl 2-methoxy-4-propenylphenoxyisobutyrate, b.p. 128—132° C./0.3 mm.; ethyl 4-(α -dimethyl-n-butyl)phenoxyisobutyrate, b.p. 127° C./0.7 mm.; ethyl 4-benzylphenoxyisobutyrate b.p. 149—152° C./0.5 mm.; ethyl 2-phenylphenoxyisobutyrate, b.p. 126° C./0.2 mm.; ethyl 4-anilinophenoxyisobutyrate, b.p. 185—190° C./0.5 mm.; ethyl 4-benzoyloxyphenoxyisobutyrate, b.p. 180—190° C./0.6 mm.; 4-benzoyloxyphenoxyisobutyric acid, m.p. 134—135° C.; 1-p-chloroanilinocyclohexane carboxylic acid, m.p. 159° C.; 2-chloroanilinoisobutyric acid, m.p. 87—88° C.; n-butyl 4-chlorophenoxyisobutyrate, b.p. 178—182° C./15 mm.; n-propyl 4-chlorophenoxyisobutyrate, b.p. 167—169° C./15 mm.; methyl 4-chlorophenoxyisobutyrate, b.p. 148—150° C./20 mm.

The pharmaceutical compositions may be formulated so as to be suitable for oral administration. For such purposes the active ingredient can be mixed with suitable known pharmaceutical excipients and incorporated by known means into such formulations as tablets, capsules, suspensions, emulsions, dispersible powders, syrups or elixirs.

Active ingredients which are liquids at ordinary temperatures may be formulated as oil-in-water or water-in-oil emulsions wherein the active ingredient itself or a solution of the active ingredient in an orally-acceptable oil for example maize oil or cod liver oil constitutes the oil phase. The solvent oil may itself be of use in the treatment of atherosclerosis for example sunflower seed oil. Emulsions are prepared with the aid of emulsifying agents, examples of which are sorbitan trioleate, polyoxyethylene sorbitan mono-oleate, lecithin, gum acacia and gum tragacanth. The emulsions may contain in addition preservatives, antioxidants, flavouring and sweetening agents and colouring materials.

Active ingredients which are sparingly soluble in water for example p-chlorophenoxyisobutyric acid and its calcium salt may be

formulated as suspensions either in an aqueous base or in an emulsion base. Aqueous based suspensions are prepared with the aid of wetting agents for example polyethyleneoxide condensation products of alkyl phenols, fatty alcohols or fatty acids and suspending agents for example hydrophilic colloids such as polyvinylpyrrolidone. Emulsion-based suspensions are prepared by suspending the active ingredient with the aid of wetting agents and suspending agents in the emulsion base which is prepared with the aid of emulsifying agents such as those described above. The suspension formulations may in addition contain sweetening agents, flavouring agents, colouring materials and preservatives.

Syrups or elixirs suitable for oral administration may be prepared from water-soluble salts for example potassium p-chlorophenoxyisobutyrate and may advantageously contain glycerol and ethyl alcohol as solvents or preservatives. They may in addition contain sweetening agents and flavouring agents for example essential oils and colouring materials.

Liquid or solid formulations may be filled into capsules for oral administration. Active ingredients which are liquids may be dissolved in oils of vegetable or animal origin, for example sunflower seed oil, maize oil or cod-liver oil and may contain additional ingredients for example antioxidants such as wheat germ oil. Solid formulations suitable for filling into capsules may contain the solid active ingredient for example p-chlorophenoxyisobutyric acid in admixture with solid materials which have a buffering action for example colloidal aluminium hydroxide or calcium hydrogen phosphate.

Formulations of the compositions of the invention as tablets in which may be coated and either effervescent or non-effervescent may be carried out according to the known art. Inert diluents or carriers for example magnesium carbonate or lactose are used together with conventional disintegrating agents for example maize starch and alginic acid and lubricating agents for example magnesium stearate.

Compositions of the invention may also be in the form of a nutritive preparation in which the active ingredient is mixed with proteins, for example casein, and carbohydrates.

The compositions of the invention may in addition contain dietary supplements for example vitamins, salts of glycerophosphoric acid, choline and inositol, the combination of which is known to be effective in reducing serum cholesterol levels, amino acids for example methionine which has a lipotropic action similar to choline and hormones or hormone extracts which may be useful in the treatment of conditions associated with old age.

As indicated above the compositions of the invention are useful in the treatment of coronary artery disease and atherosclerosis. It is

expected that the compositions will generally be administered orally in the form of capsules containing between about 0.1 and 1.0 gm. of liquid or solid active ingredient or in the form of tablets, either effervescent or non-effervescent, containing between about 0.1 and 3.0 gm. of solid active ingredient, these compositions being administered such that a patient undergoing treatment receives a daily dosage of between about 1.0 and 10 gm. of active ingredient.

The invention is illustrated but not limited by the following Examples 1—15 in which the parts are by weight:—

EXAMPLE 1:

A solution of 200 parts of cane sugar, 1 part of sodium benzoate, 0.6 part of pyridoxine hydrochloride and 10 parts of a polyethylene sorbitan mono-oleate condensate in 400 parts of water is added slowly to a stirred mixture of 500 parts of ethyl p-chlorophenoxyisobutyrate, 25 parts of refined soya bean lecithin, 2.4 parts of a mixed tocopherols concentrate and 0.05 part of propyl gallate. The resulting emulsion is homogenised by passage through a conventional homogeniser and there is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

The ethyl p-chlorophenoxyisobutyrate used as starting material may be obtained by heating a mixture of 206 parts of dry p-chlorophenoxyisobutyric acid, 1000 parts of ethanol and 40 parts of concentrated sulphuric acid under reflux during 5 hours. The alcohol is then distilled off and the residue is diluted with water and extracted with chloroform. The chloroform extract is washed with sodium hydrogen carbonate solution, dried over sodium sulphate and the chloroform removed by distillation. The residue is distilled under reduced pressure and there is obtained ethyl p-chlorophenoxyisobutyrate, b.p. 148—150° C./20 mm.

EXAMPLE 2:

To a stirred solution of 200 parts of ethyl p-chlorophenoxyisobutyrate, 5 parts of a mixed tocopherol concentrate, 0.1 part of propyl gallate, 50 parts of a polyoxyethylene sorbitan mono-oleate condensate, and 50 parts of sorbitan tri-oleate in 500 parts of maize oil is added a solution of 54 parts of sodium cyclamate, 1 part of pyridoxine hydrochloride, 3 parts of methyl p-hydroxybenzoate and 1 part of propyl p-hydroxybenzoate in 960 parts of water. A suitable flavouring agent is incorporated in the mixture which is then homogenised by passage through a conventional homogeniser. There is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

EXAMPLE 3:

To a mixture of 40 parts of p-chlorophenoxyisobutyric acid and 33.7 parts of liquid paraffin are added 3 parts of gum acacia and 1.5 parts of gum tragacanth. To the

thoroughly triturated mixture is added slowly with stirring a solution of 0.1 part of a cetyl alcohol polyoxyethylene condensate, 40 parts of cane sugar, 0.03 part of propyl p-hydroxybenzoate, 0.3 part of methyl p-hydroxybenzoate and 0.002 part of edible dyestuff in 110 parts of water. After the incorporation of a suitable flavouring agent, the mixture is homogenised by passage through a conventional homogeniser and there is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

The p-chlorophenoxyisobutyric acid used as starting material may be obtained as follows: A mixture of 200 parts of p-chlorophenol, 1000 parts of acetone and 360 parts of sodium hydroxide pellets is heated under reflux and 240 parts of chloroform are gradually added at such a rate that the mixture continues to reflux without further application of heat. When addition is complete the mixture is heated under reflux during 5 hours and then the acetone is removed by distillation. The residue is dissolved in water, acidified with hydrochloric acid and the mixture extracted with chloroform. The chloroform extract is stirred with sodium hydrogen carbonate solution and the aqueous layer is separated. The alkaline extract is acidified with hydrochloric acid and filtered. The solid product is drained free from oil on a filter pump, then washed with petroleum ether (b.p. 40—60° C.), and dried at 50° C. The solid residue, m.p. 114—116° C., may be crystallised from methanol (with the addition of charcoal) to give p-chlorophenoxyisobutyric acid, m.p. 118—119° C.

EXAMPLE 4:

In a similar manner to that described in Example 3 but replacing the 33.7 parts of liquid paraffin by 30 parts of maize oil containing 0.01 part of propyl gallate, there is obtained an emulsion suitable for oral administration for therapeutic purposes.

EXAMPLE 5:

100 Parts of calcium p-chlorophenoxyisobutyrate are added to a solution of 15 parts of calcium cyclamate, 2 parts of a condensation product of octylcresol with 8—10 molecular proportions of ethylene oxide, 3 parts of polyvinyl pyrrolidone and 0.9 part of methyl p-hydroxybenzoate in 500 parts of water. The mixture is ball-milled for several hours and after the incorporation of a suitable flavouring agent there is obtained a suspension suitable for oral administration for therapeutic purposes.

EXAMPLE 6:

A mixture of 40 parts of p-chlorophenoxyisobutyric acid, 40 parts of sucrose, 0.5 part of a cetyl alcohol polyethylene oxide condensate, 1 part of polyvinyl pyrrolidone, 0.25 part of methyl p-hydroxybenzoate and 100 parts of water is ball-milled for several hours. After the incorporation of suitable colouring

and flavouring agents there is obtained a suspension suitable for oral administration for therapeutic purposes.

EXAMPLE 7:

- 5 200 Parts of potassium p-chlorophenoxyisobutyrate are dissolved in a mixture of 83 parts of water, 250 parts of glycerol and 125 parts of ethyl alcohol. To the resultant solution is added a solution of 300 parts of sucrose
10 in 150 parts of water. By the incorporation of a suitable flavouring agent and colouring matter, there is obtained a syrup suitable for oral administration for therapeutic purposes.

EXAMPLE 8:

- 15 200 Parts of ethyl p-chlorophenoxyisobutyrate and 5 parts of wheat germ oil are dissolved in 750 parts of sunflower seed oil. The solution is filled into gelatine capsules which are then suitable for oral administration
20 for therapeutic purposes.

EXAMPLE 9:

- 25 25 Parts of sodium glycerophosphate, 25 parts of calcium glycerophosphate and 50 parts of calcium p-chlorophenoxyisobutyrate are intimately mixed. The mixture is added gradually to 900 parts of soluble casein in a conventional mixer and mixing continued until homogeneous. There is thus obtained a dietary supplement suitable for oral administration for therapeutic purposes.
30

EXAMPLE 10:

- An intimate mixture is prepared with conventional mixing equipment of 3 parts of pyridoxine hydrochloride, 100 parts of nicotinic acid, 100 parts of nicotinamide, 5 parts of methionine, 15 parts of choline bitartrate, 150 parts of ascorbic acid, 5 parts of calcium pantothenate, 10 parts of riboflavin and 1000 parts of calcium p-chlorophenoxyisobutyrate. The mixture is filled into capsules which are then suitable for oral administration for therapeutic purposes.
35
40

EXAMPLE 11:

- 45 A mixture of 500 parts of calcium p-chlorophenoxyisobutyrate, 94 parts of maize starch, 45 parts of alginic acid and 3.5 parts of magnesium stearate, is compressed into slugs which are then broken into granules. The granules are passed through an 8-mesh screen and 3.5 parts of magnesium stearate are added. The mixture is then compressed into tablets which are suitable for oral administration for therapeutic purposes.
50

EXAMPLE 12:

- 55 A mixture of 1 part of sodium di-octyl sulposuccinate dissolved in a sufficient quantity of methanol, 500 parts of calcium p-chlorophenoxyisobutyrate, 75 parts of maize starch and 5 parts of alginic acid is granulated by admixture with a sufficient quantity of aqueous 10% maize starch paste. The granules are passed through a 12-mesh screen and dried at 50—55° C. The granules are then again passed through a 12-mesh screen
60
65 and 6 parts of magnesium stearate are added

and the mixture is compressed. There are thus obtained tablets suitable for oral administration for therapeutic purposes.

EXAMPLE 13:

A mixture of 500 parts of potassium p-chlorophenoxyisobutyrate, 50 parts of light magnesium carbonate and 10 parts of magnesium stearate is compressed into slugs. The slugs are broken into granules which are passed through an 8-mesh screen and compressed. There are thus obtained tablets suitable for oral administration for therapeutic purposes.
70
75

EXAMPLE 14:

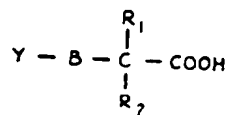
A mixture of 500 parts of potassium p-chlorophenoxyisobutyrate and 50 parts of light magnesium carbonate is granulated by admixture with a solution of 2 parts of sodium di-octyl sulposuccinate in a sufficient quantity of methanol. The granules are passed through a 12-mesh screen and dried at 50—55° C. The granules are then again passed through a 12-mesh screen and 8 parts of magnesium stearate are added and the mixture is compressed. There are thus obtained tablets suitable for oral administration for therapeutic purposes.
80
85
90

EXAMPLE 15:

A mixture of 500 parts of p-chlorophenoxyisobutyric acid, 94 parts of maize starch and 3 parts of magnesium stearate is compressed into slugs. The slugs are broken into granules which are then passed through an 8-mesh screen. The granules are then coated with a sufficient quantity of a solution of 15 parts of shellac and 3 parts of castor oil in 800 parts of ethyl alcohol; 3 parts of magnesium stearate are then added to the granules after which they are compressed to give tablets suitable for oral use for therapeutic purposes.
95
100
105

It is to be understood that the solid or liquid active ingredients in the foregoing Examples 1—15 may be replaced by any of the solid or liquid active ingredients listed at the beginning of the specification.
110

Some of the compounds used as the active ingredients in the compositions of the invention have not been described in the art. However, these new compounds may be readily obtained by the use of processes well known in the art. Thus the compounds of the formula:—
115



wherein R₁ and R₂, which may be the same or different, stand for hydrogen, or for alkyl radicals or they may be joined together to form, with the adjacent carbon atom, a cycloalkyl ring, and B stands for an oxygen atom and Y stands for a dihalogenated phenyl
120

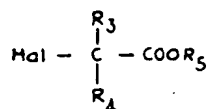
radical or for a phenyl radical containing at least one substituent selected from the group consisting of alkyl of at least two carbon atoms, alkenyl, aryl, aralkyl and arylamino radicals or for a naphthyl radical optionally substituted by one, two or three substituents which may be the same or different and which are selected from halogen atoms and alkyl, alkenyl, alkoxy, aryl, aralkyl, aralkoxy and arylamino radicals, or B stands for an imino radical and Y stands for a phenyl or naphthyl radical, optionally substituted by one, two or three substituents which may be the same or different and which are selected from halogen atoms and alkyl, alkenyl, alkoxy, aryl, aralkyl, aralkoxy and arylamino radicals, are new, but they are obtainable by the use of processes well known in the art. Thus certain of them may be prepared by interaction of the corresponding phenol or naphthol of the formula Y—OH wherein Y has the meaning stated above and a ketone of the formula



wherein R_3 and R_4 stand for alkyl radicals, the same or different, or they may be joined together to form, with the adjacent carbon atom, a cycloalkyl ring in the presence of a tri- or tetra-halogenated methane derivative and a strong base.

As a suitable tri or tetra-halogenated methane derivative there may be mentioned for example chloroform, acetonechloroform, bromoform, acetonebromoform, chloral, bromal, chloral hydrate, bromal hydrate, carbon tetrachloride or carbon tetrabromide and a suitable strong base may be sodium hydroxide or potassium hydroxide particularly in the solid form.

The process may conveniently be carried out in the presence of a diluent or solvent such as excess of the ketone used as reactant. The reaction may be accelerated or completed by the application of heat. They may also be prepared by interaction of a metal derivative of the corresponding phenol or naphthol of the formula Y—OH wherein Y has the meaning stated above and a compound of the formula:—



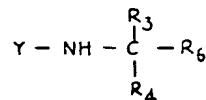
wherein R_3 and R_4 have the meaning stated above, Hal stands for a halogen atom and R_5 stands for an alkyl radical.

A suitable metal derivative may be an alkali metal derivative such as the sodium salt of the phenol or naphthol.

The process may be conveniently carried out by the application of heat and there is preferably present an inert diluent or solvent for example benzene, toluene, xylene or ethanol.

The new compounds as hereinbefore described which have a free carboxyl group may be converted into the corresponding esters or salts thereof by conventional means and likewise the esters or salts may be converted into the corresponding acids by conventional means.

The new compounds may also be prepared by hydrolysis of a compound of the formula:—



wherein R_3 and R_4 have the meaning stated above, Y stands for a phenyl or naphthyl radical optionally substituted and R_6 stands for a carboxy amide radical or for a functional derivative or precursor thereof.

As a suitable precursor of the carboxy amide derivatives there may be mentioned for example the corresponding nitriles. The hydrolysis may conveniently be carried out in the presence of concentrated aqueous hydrochloric acid preferably with application of heat.

The carboxy amides of the above stated formula used as starting materials may conveniently be obtained by hydrolysis of the corresponding nitriles in the presence of concentrated sulphuric acid at ordinary temperature. The nitriles themselves may conveniently be obtained by the addition of an aqueous solution of an alkali metal cyanide to a mixture of the corresponding ketone of the formula:—



wherein R_3 and R_4 have the meaning stated above and a primary aromatic amine of the formula:—



wherein Y stands for a phenyl or naphthyl radical optionally substituted in the presence of glacial acetic acid.

Illustrated procedures for the preparation of the new compounds are given in the following Examples 16—21 in which the parts are by weight:—

EXAMPLE 16:

A mixture of 50 parts of p-ethylphenol, 400 parts of acetone and 90 parts of sodium hydroxide pellets is heated under reflux and 60 parts of chloroform are gradually added at such a rate that the mixture continues to reflux without further application of heat. When addition is complete the mixture is heated under reflux during 5 hours and then the acetone is removed by distillation. The residue is dissolved in water, acidified with aqueous hydrochloric acid and the mixture extracted with chloroform. The chloroform extract is stirred with sodium hydrogen carbonate solution and the aqueous layer is separated. The alkaline extract is acidified with

aqueous hydrochloric acid and filtered. The solid residue is crystallised from benzene to give 4-ethylphenoxyisobutyric acid, m.p. 77—78° C.

- 5 In a similar manner, 4-tertiary-butylphenoxyisobutyric acid, m.p. 93—94° C. (crystallised from petroleum ether b.p. 40—60° C.) is obtained from p-tertiary butylphenol; and 10 4-phenylphenoxyisobutyric acid, m.p. 167—168° C. (crystallised from benzene) is obtained from 4-hydroxydiphenyl; 4-tertiary-octylphenoxyisobutyric acid, m.p. 89—90° C. (crystallised from petroleum ether b.p. 40—60° C.) is obtained from 4-tertiary octyl 15 phenol; 3-methyl-4-chlorophenoxyisobutyric acid, m.p. 85—86° C. (crystallised from chloroform) is obtained from 2-chloro-5-hydroxytoluene; and 2-methoxyphenoxyisobutyric acid, b.p. 120—130° C./0.3 mm., 20 m.p. 45—47° C. is obtained from guaiacol.

EXAMPLE 17:

- A mixture of 50 parts of eugenol, 400 parts of acetone and 90 parts of sodium hydroxide pellets is heated under reflux and 60 parts of 25 chloroform are gradually added at such a rate that the mixture continues to reflux without further application of heat. When the addition of chloroform is complete, the mixture is heated under reflux during 5 hours. The reaction mixture is treated in the manner as 30 described in Example 1 and there is obtained a crude acid in the form of an oil. This crude acid is heated under reflux with 250 parts of ethanol and 10 parts of concentrated sulphuric acid for 4 hours. The mixture is cooled, 35 diluted with water and extracted with ether. The ethereal extract is washed with sodium hydrogen carbonate solution and water, and then dried over sodium sulphate. The solvent 40 is removed by distillation and the residue is distilled under reduced pressure and there is obtained ethyl (2-methoxy-4-allylphenoxy)isobutyrate, b.p. 118—120° C./0.2 mm.

- In a similar manner, ethyl (o-benzylphenoxy)isobutyrate, b.p. 152—156° C./0.4 mm. 45 is obtained from o-benzylphenol; ethyl 3:4-dichlorophenoxyisobutyrate, b.p. 104° C./0.2 mm. is obtained from 3:4-dichlorophenol; ethyl 2 methoxy-4-propenylphenoxyisobutyrate b.p. 128—132° C./0.3 mm. is obtained 50 from isoeugenol; and ethyl 4-(α -dimethyl-n-butyl)phenoxyisobutyrate, b.p. 127° C./0.7 mm. is obtained from 4-(α -dimethyl-n-butyl)-phenol.

EXAMPLE 18:

- 18.4 Parts of p-benzylphenol and 200 parts of dry xylene are heated under reflux and 2.3 55 parts of sodium are added and heating is continued during 4 hours. 23 Parts of ethyl α -bromo-isobutyrate are then added and the mixture is then heated under reflux for a 60 further 5 hours. The mixture is cooled, diluted with water and extracted with ether. The extract is dried over sodium sulphate and 65 the solvents are removed by distillation and

the residue is then distilled under reduced pressure. There is thus obtained ethyl (4-benzylphenoxy)-isobutyrate, b.p. 149—152° C./0.5 mm.

In a similar manner, ethyl (2-phenylphenoxy)isobutyrate, b.p. 126° C./0.2 mm. is obtained from 2-hydroxydiphenyl; ethyl (4-anilinophenoxy)isobutyrate, b.p. 185—190° C./0.5 mm. (hydrochloride, m.p. 171—172° C. with decomposition when crystallised from ethanol) is obtained from 4-hydroxydiphenylamine; and ethyl 4-benzyloxyphenoxyisobutyrate, b.p. 180—190° C./0.6 mm. is obtained from hydroquinone monobenzyl ether, and is hydrolysed by heating with potassium hydroxide in methanol to 4-benzyloxyphenoxyisobutyric acid, m.p. 134—135° C. after crystallisation from benzene.

EXAMPLE 19:

A mixture of 27 parts of dry 4-chlorophenoxyisobutyric acid, 250 parts of n-butanol and 18 parts of concentrated sulphuric acid are boiled under reflux for 16 hours, and the water formed during the reaction is removed continuously by means of a suitable take-off 70 apparatus. The butanol is removed by distillation under reduced pressure and the residue diluted with water and extracted with ether. The ether solution is washed with dilute sodium hydroxide solution, then with water, and 75 dried over sodium sulphate, and the ether removed by distillation. The residue is distilled under reduced pressure giving n-butyl 4-chlorophenoxyisobutyrate, b.p. 178—182° C./15 mm. 80 100

In a similar way n-propyl 4-chlorophenoxyisobutyrate b.p. 167—169° C./15 mm. is obtained from 4-chlorophenoxyisobutyric acid and n-propanol.

EXAMPLE 20:

9 Parts of 4-chlorophenoxyisobutyric acid are added to a solution of excess diazomethane in ether, and the mixture is left at room temperature overnight. The ether is removed by distillation and the residue distilled under reduced pressure giving methyl 4-chlorophenoxyisobutyrate, b.p. 148—150° C./20 mm. 105 110

EXAMPLE 21:

A mixture of 43 parts α -p-chloroanilinoisobutyramide and 200 parts of concentrated aqueous hydrochloric acid is heated at 95—100° C. during 18 hours. It is then cooled and filtered. The solid residue is treated with hot dilute aqueous sodium hydroxide and filtered. The filtrate is acidified with acetic acid and the mixture is filtered. The solid residue is crystallised from benzene and there is obtained 4-chloroanilinoisobutyric acid, m.p. 142—143° C. 115 120

The α -p-chloroanilinoisobutyramide used as starting material in the above process may be obtained by stirring 40 parts of α -p-chloroanilinoisobutyronitrile and 100 parts of concentrated sulphuric acid at 18—22° C. during 18 hours. The mixture is poured on ice and 130

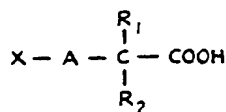
basified with ammonium hydroxide. The mixture is filtered and the solid residue is crystallised from benzene to give α -p-chloroanilino-isobutyramide, m.p. 137—138° C. The α -p-chloroanilino-isobutyronitrile itself may be obtained by stirring a mixture of 70 parts of acetone, 127 parts of p-chloroaniline and 400 parts of glacial acetic acid, cooled in ice, while a solution of 49 parts of sodium cyanide in 100 parts of water is gradually added. The mixture is stirred for 1 hour and filtered. The solid residue is washed with water and dried. It is then crystallised from methanol to give α -p-chloroanilino-isobutyronitrile, m.p. 95° C.

- 15 In a similar way 1-p-chloroanilinocyclohexane carboxyamide on hydrolysis with concentrated hydrochloric acid gives 1-p-chloroanilinocyclohexane carboxylic acid, m.p. 159° C. after crystallisation from methanol. The 1-p-chloroanilinocyclohexane carboxyamide used as starting material may be obtained from 1-cyano-1-p-chloroanilinocyclohexane by treatment with concentrated sulphuric acid and has m.p. 170° C. The 1-cyano-1-p-chloroanilinocyclohexane itself may be obtained by treating cyclohexanone and p-chloroaniline in glacial acetic acid with a solution of sodium cyanide, and has m.p. 112° C.

- 30 Similarly, 2-chloroanilinoisobutyric acid m.p. 87—88° C. (from benzene/petroleum ether) is obtained by an analogous series of reactions starting from acetone, o-chloroaniline and sodium cyanide. The corresponding α -2-chloroanilinoisobutyramide and α -2-chloroanilinoisobutyronitrile were not however obtained solid.

WHAT WE CLAIM IS:—

- 1) Pharmaceutical compositions containing as active ingredient at least one compound of the formula:—



wherein A stands for oxygen or for the imino radical, R₁ and R₂, which may be the same or different, stand for hydrogen or for alkyl radicals, or they may be joined to form, together with the adjacent carbon atom, a

cycloalkyl ring, and X stands for a phenyl or naphthyl radical which may optionally be substituted by one, two or three substituents which may be the same or different and which are selected from halogen atoms and alkyl, alkenyl, alkoxy, aryl, aralkyl, aralkoxy, and arylamino radicals, or the esters or salts thereof, together with a non-toxic pharmaceutically-acceptable inert diluent or carrier, provided that the inert diluent or carrier is not water or an organic solvent.

2) Compositions as claimed in Claim 1 wherein R₁ and/or R₂ are methyl or ethyl radicals.

3) Compositions as claimed in Claim 1 wherein R₁ and R₂, together with the adjacent carbon atoms, stand for a cyclohexane ring.

4) Compositions as claimed in Claim 1 wherein the ester is a methyl, ethyl or n-propyl ester.

5) Compositions as claimed in Claim 1 wherein the salts are alkali metal or alkaline earth metal salts, or acid-addition salts.

6) Compositions as claimed in Claim 1 wherein the active ingredient is p-chlorophenoxyisobutyric acid or an ester or a salt thereof.

7) Compositions as claimed in any of Claims 1—6 which are formulated for oral administration.

8) Compositions as claimed in Claim 7 which are in the form of tablets, capsules, suspensions, emulsions, dispersible powders, syrups or elixirs.

9) Compositions as claimed in any of Claims 1—8 which are in the form of a nutritive preparation wherein the active ingredient is mixed with proteins and carbohydrates.

10) Compositions as claimed in any of Claims 1—9 wherein there is present a dietary supplement for example vitamins, salts of glycerophosphoric acid, choline and inositol, amino acids or hormones or hormone extracts.

11) Pharmaceutical compositions, claimed in Claims 1—10, as hereinbefore particularly described and especially with reference to the foregoing Examples 1—15.

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PROVISIONAL SPECIFICATION

Pharmaceutical Compositions comprising α -Aryloxy-Aliphatic Carboxylic Acids and/or α -Arylimino-Aliphatic Carboxylic Acids, their Esters and Salts

We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare this invention to be described in the following statement:—

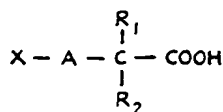
This invention relates to new pharmaceu-

tical compositions and more particularly it relates to pharmaceutical compositions which possess valuable therapeutic properties.

It is believed that certain diseases such as coronary artery disease and atherosclerosis in man are associated with an abnormally high

concentration of cholesterol in the blood serum. We have now found that certain aryl derivatives of aliphatic acids reduce the concentration of cholesterol in the blood serum, and there may therefore be useful in the treatment of such diseases as coronary artery disease and atherosclerosis.

According to the invention we provide new pharmaceutical compositions containing as active ingredient at least one compound of the formula:—



wherein A stands for oxygen or for an imino radical, R₁ and R₂ which may be the same or different, stand for hydrogen, or for alkyl radicals or they may be joined to form, together with the adjacent carbon atom, a cycloalkyl ring, and X stands for a phenyl or naphthyl radical which may optionally be substituted, or the esters or salts thereof, in the presence of a non-toxic pharmaceutically-acceptable inert diluent or carrier therefor.

As particularly suitable alkyl radicals (R₁ and R₂) there may be mentioned for example methyl and ethyl radicals and a suitable cycloalkyl ring may be the cyclohexane ring. Optional substituents in the phenyl or naphthyl radical may be halogen, alkyl, alkenyl, alkoxy, aryl, aralkyl or arylamino radicals. Preferred esters of the above described acids are methyl and ethyl esters and suitable salts of the said acids may be the alkali metal or alkaline earth metal salts such as the sodium potassium or calcium salts or, when the acids possess a strongly basic substituent, the acid-addition salts thereof such as the hydrochlorides.

Preferred compounds to be used as the active ingredient in the composition of the invention are p-chlorophenoxyisobutyric acid and the esters and salts thereof such as the methyl and ethyl esters and the alkali metal and alkaline earth metal salts such as the potassium salt which is soluble in water and the calcium salt which is sparingly soluble in water.

The new pharmaceutical compositions may be formulated so as to be suitable for oral administration. For such purposes the active ingredient can be mixed with suitable known pharmaceutical excipients and incorporated by known means into such formulations as tablets, capsules, suspensions, emulsions, solutions or dispersible powders.

Active ingredients which are liquids at ordinary temperatures may be formulated as emulsions wherein the active ingredient itself or a solution of the active ingredient in an orally-acceptable oil for example maize oil or cod liver oil constitutes the oil phase. The

solvent oil may itself be of use in the treatment of atherosclerosis for example sunflower seed oil. Emulsions are prepared with the aid of emulsifying agents examples of which are sorbitan tri-oleate polyoxyethylene sorbitan mono-oleate, lecithin, gum acacia and gum tragacanth. The emulsions may contain in addition preservatives, anti-oxidants, flavouring and sweetening agents and colouring materials.

Active ingredients which are sparingly soluble in water for example p-chlorophenoxyisobutyric acid and its calcium salt may be formulated as suspensions either in an aqueous base or in an emulsion base. Aqueous based suspensions are prepared with the aid of wetting agents for example polyethyleneoxide condensation products of alkyl phenols, fatty alcohols or fatty acids and suspending agents for example hydrophilic colloids such as polyvinylpyrrolidone. Emulsion-based suspensions are prepared by suspending the active ingredient with the aid of wetting agents and suspending agents in the emulsion base which is prepared with the aid of emulsifying agents such as those described above. The suspension formulations may in addition contain sweetening agents, flavouring agents, colouring materials, preservatives and antioxidants.

Syrups or elixirs suitable for oral administration may be prepared from water-soluble salts for example potassium p-chlorophenoxyisobutyrate and may advantageously contain glycerol and ethyl alcohol as solvents or preservatives. They may in addition contain sweetening agents and flavouring agents for example essential oils and colouring materials.

Liquid or solid formulations may be filled into capsules for oral administration. Active ingredients which are liquids may be dissolved in oils of vegetable or animal origin for example sunflower seed oil, maize oil or cod-liver oil and may contain additional ingredients for example antioxidants such as wheat germ oil. Solid formulations suitable for filling into capsules may contain the solid active ingredient for example p-chlorophenoxyisobutyric acid in admixture with solid materials which have a buffering action for example colloidal aluminium hydroxide or calcium hydrogen phosphate.

Formulations of the compositions of the invention as tablets which may be coated may be carried out according to the known art. Inert diluents or carriers for example magnesium carbonate or lactose are used together with conventional disintegrating agents for example maize starch and alginic acid and lubricating agents for example magnesium stearate.

Compositions of the invention may also be in the form of a nutritive preparation in which the active ingredient is mixed with proteins and carbohydrates for example casein.

The compositions described above may in addition contain dietary supplements for example vitamins, salts of glycerophosphoric acid, choline and inositol the combination of which is known to be effective in reducing serum cholesterol levels, amino acids for example methionine which has a lipotropic action similar to choline and hormones or hormone extracts which may be useful in the treatment of conditions associated with old age.

The invention is illustrated but not limited by the following Examples in which the parts are by weight:—

EXAMPLE 1:

A solution of 200 parts of cane sugar, 1 part of sodium benzoate, 0.6 part of pyridoxine hydrochloride and 10 parts of a polyoxyethylene sorbitan mono-oleate condensate in 400 parts of water is added slowly to a stirred mixture of 500 parts of ethyl p-chlorophenoxy isobutyrate, 25 parts of refined soya bean lecithin, 2.4 parts of a mixed tocopherols concentrate and 0.05 part of propyl gallate. The resultant emulsion is homogenised by passage through a conventional homogeniser and there is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

The ethyl p-chlorophenoxyisobutyrate used as starting material may be obtained by heating a mixture of 206 parts of dry p-chlorophenoxyisobutyric acid, 1000 parts of ethanol and 40 parts of concentrated sulphuric acid under reflux for 5 hours. The alcohol is then distilled off and the residue is diluted with water and extracted with chloroform. The chloroform extract is washed with sodium hydrogen carbonate solution, dried over sodium sulphate and the chloroform removed by distillation. The residue is distilled under reduced pressure and there is obtained ethyl p-chlorophenoxyisobutyrate, b.p. 148—150° C./20 mm.

EXAMPLE 2:

To a stirred solution of 200 parts of ethyl p-chlorophenoxyisobutyrate, 5 parts of a mixed tocopherol concentrate, 0.1 part of propyl gallate, 50 parts of a polyoxyethylene sorbitan mono-oleate condensate, and 50 parts of sorbitan tri-oleate in 500 parts of maize oil is added to a solution of 54 parts of sodium cyclamate, 1 part of pyridoxine hydrochloride, 3 parts of methyl p-hydroxybenzoate and 1 part of propyl p-hydroxybenzoate in 960 parts of water. A suitable flavouring agent is incorporated in the mixture which is then homogenised by passage through a conventional homogeniser. There is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

EXAMPLE 3:

To a mixture of 40 parts of p-chlorophenoxyisobutyric acid and 33.7 parts of liquid paraffin are added 3 parts of gum

acacia and 1.5 parts of gum tragacanth. To the thoroughly triturated mixture is added slowly with stirring a solution of 0.1 part of a cetyl alcohol polyoxyethylene condensate, 40 parts of cane sugar, 0.03 part of propyl p-hydroxybenzoate, 0.3 part of methyl p-hydroxybenzoate and 0.002 part of edible dye-stuff in 110 parts of water. After the incorporation of a suitable flavouring agent, the mixture is homogenised by passage through a conventional homogeniser and there is thus obtained an emulsion suitable for oral administration for therapeutic purposes.

The p-chlorophenoxyisobutyric acid used as starting material may be obtained as follows: A mixture of 200 parts of p-chlorophenol, 1000 parts of acetone and 360 parts of sodium hydroxide pellets is heated under reflux and 240 parts of chloroform are gradually added at such a rate that the mixture continues to reflux without further application of heat. When addition is complete the mixture is heated under reflux during 5 hours and then the acetone is removed by distillation. The residue is dissolved in water, acidified with hydrochloric acid and the mixture extracted with chloroform. The chloroform extract is stirred with sodium hydrogen carbonate solution and the aqueous layer is separated. The alkaline extract is acidified with hydrochloric acid and filtered. The solid product is drained free from oil on a filter pump, then washed with petroleum ether (b.p. 40—60° C.), and dried at 50° C. The solid residue m.p. 114—116° C. may be crystallised from methanol (with the addition of charcoal) to give p-chlorophenoxyisobutyric acid, m.p. 118—119° C.

EXAMPLE 4:

In a similar manner as that described in Example 3 but replacing the 33.7 parts of liquid paraffin by 30 parts of maize oil containing 0.01 part of propyl gallate, there is obtained an emulsion suitable for oral administration for therapeutic purposes.

EXAMPLE 5:

100 Parts of calcium p-chlorophenoxyisobutyrate are added to a solution of 15 parts of calcium cyclamate, 2 parts of a condensation product of octylcresol with 8—10 molecular proportions of ethylene oxide, 3 parts of polyvinyl pyrrolidone and 0.9 part of methyl p-hydroxybenzoate in 500 parts of water. The mixture is ball-milled for several hours and after the incorporation of a suitable flavouring agent there is obtained a suspension suitable for oral administration for therapeutic purposes.

EXAMPLE 6:

A mixture of 40 parts of p-chlorophenoxyisobutyric acid, 40 parts of sucrose, 0.5 part of a cetyl alcohol polyethylene oxide condensate, 1 part of polyvinyl pyrrolidone, 0.25 part of methyl p-hydroxybenzoate and 100 parts of water is ball-milled for several hours.

After the incorporation of suitable colouring and flavouring agents there is obtained a suspension suitable for oral administration for therapeutic purposes.

5 EXAMPLE 7:

200 Parts of potassium p-chlorophenoxyisobutyrate are dissolved in a mixture of 83 parts of water, 250 parts of glycerol and 125 parts of ethyl alcohol. To the resultant solution 10 added a solution of 300 parts of sucrose in 750 parts of water. By the incorporation of a suitable flavouring agent and colouring matter there is obtained a syrup 15 suitable for oral administration for therapeutic purposes.

 EXAMPLE 8:

200 Parts of ethyl p-chlorophenoxyisobutyrate and 5 parts of wheat germ oil are dissolved in 750 parts of sunflower seed oil. 20 The solution is filled into gelatin capsules which are then suitable for oral administration for therapeutic purposes.

 EXAMPLE 9:

25 Parts of sodium glycerophosphate, 25 parts of calcium glycerophosphate and 50 parts of calcium p-chlorophenoxyisobutyrate are intimately mixed. The mixture is added 25 gradually to 900 parts of soluble casein in a conventional mixer and mixing continued until 30 homogeneous. There is thus obtained a dietary supplement suitable for oral administration for therapeutic purposes.

 EXAMPLE 10:

An intimate mixture is prepared with conventional mixing equipment of 3 parts of 35 pyridoxine hydrochloride, 100 parts of nicotinic acid, 100 parts of nicotinamide, 5 parts of methionine, 15 parts of choline bitartrate, 150 parts of ascorbic acid, 5 parts of calcium 40 pantothenate, 10 parts of riboflavin and 1000 parts of calcium p-chlorophenoxyisobutyrate. The mixture is filled into capsules which are then suitable for oral administration for therapeutic purposes.

45 EXAMPLE 11:

A mixture of 500 parts of calcium p-chlorophenoxyisobutyrate, 94 parts of maize starch, 45 parts of alginic acid and 3.5 parts of magnesium stearate, is compressed into slugs which 50 are then broken into granules. The granules are passed through an 8-mesh screen and 3.5 parts of magnesium stearate are added. The mixture is then compressed into tablets which 55 are suitable for oral administration for therapeutic purposes.

EXAMPLE 12:

A mixture of 1 part of sodium di-octyl sulphosuccinate dissolved in a sufficient quantity of methanol, 500 parts of calcium p-chlorophenoxyisobutyrate, 75 parts of maize 60 starch and 5 parts of alginic acid is granulated by admixture with a sufficient quantity of aqueous 10% maize starch paste. The granules are then again passed through a 12-mesh 65 screen and dried at 50—55° C. The granules are then again passed through a 12-mesh screen and 6 parts of magnesium stearate are added and the mixture is compressed. There are thus obtained tablets suitable for oral 70 administration for therapeutic purposes.

EXAMPLE 13:

A mixture of 500 parts of potassium p-chlorophenoxyisobutyrate, 50 parts of light magnesium carbonate and 10 parts of magnesium stearate is compressed into slugs. The 75 slugs are broken into granules which are passed through an 8-mesh screen and then compressed. There are thus obtained tablets suitable for oral administration for therapeutic purposes. 80

EXAMPLE 14:

A mixture of 500 parts of potassium p-chlorophenoxyisobutyrate and 50 parts of light magnesium carbonate is granulated by admixture with a solution of 2 parts of sodium di-octyl sulphosuccinate in a sufficient 85 quantity of methanol. The granules are passed through a 12-mesh screen and dried at 50—55° C. The granules are then again passed through a 12-mesh screen and 8 parts of 90 magnesium stearate are added and the mixture is compressed. There are thus obtained tablets suitable for oral administration for therapeutic purposes.

EXAMPLE 15:

A mixture of 500 parts of p-chlorophenoxyisobutyric acid, 94 parts of maize starch and 3 parts of magnesium stearate is compressed into slugs. The slugs are broken into granules which are then passed through an 8-mesh screen. The granules are then coated 100 with a sufficient quantity of a solution of 15 parts of shellac and 2 parts of castor oil in 800 parts of ethyl alcohol, 3 parts of magnesium stearate and then added to the granules after which they are compressed to give 105 tablets suitable for oral use for therapeutic purposes.

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